Docket No. 44470-C1-CPA-C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	H. Wong et al.		
SERIAL NO.:	09/900,379	EXAMINER:	Vander Vegt, F.
FILED:	July 6, 2001	GROUP:	1644
FOR:			

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

DECLARATION OF PETER R. RHODE PURSUANT TO 37 CFR 1.132

I, Peter R. Rhode, declare as follows:

1. I am a co-inventor on the above-identified application (hereafter the "subject application"). I am presently Vice President of Research and Development at Altor BioScience Corporation, a biotechnology company based in Miramar, Florida. Prior to that position, I was Senior Scientist with Sunol Molecular Corporation. I have also held the positions of Senior Scientist and Scientist with Dade International Inc. and Baxter Healthcare Inc. I hold a Ph.D. degree in Biochemistry from the University of Wisconsin, Madison and was a Senior Research Fellow at the California Institute of Technology.

2. The subject application discloses and claims, among other things, multivalent MHC fusion complexes that include two or more linked MHC fusion complexes. As I understand it, the MHC fusion molecule includes a peptide-binding groove and a presenting peptide covalently linked to the MHC peptide and positioned such that the presenting peptide can work. The MHC fusion molecule further includes a linker sequence interposed between the MHC molecule and the presenting peptide. In addition, the MHC fusion molecule further includes a leader sequence attached to the presenting peptide.

3. I have found that the interposed linker sequence can be important to provide a functional MHC complex with a covalently linked presenting peptide. In particular, the

interposed linker effectively positions the covalently linked presenting peptide, e.g. so that the presenting peptide can modulate the activity of the MHC complex and larger multivalent complex. Thus, as disclosed at page 13, line 11 through page 14, line 28 of the subject application, in a class II MHC molecule, a linker is required to position the linked presenting peptide into the binding groove formed by the α and β chains.

4. Additionally, I have found that the leader sequence is required for the generation of functional multivalent MHC fusion complex. In particular, the leader sequence provides for secretory expression of the MHC fusion complex, thus facilitating soluble production. In addition, the leader sequence contains restriction sites to ease vector construction, as well as strong translation initiation and RNA processing sites to improve the expression of the MHC fusion complex. These and other benefits of the leader sequence are disclosed on pages 17-18, 78-79 and Figure 18B of the subject application.

5. I have reviewed the Patent Office Action ("Office Action") dated July 1, 2003 issued in connection with the subject application. As I understand the Office Action, the patent Examiner has rejected certain claims of the application in view of documents that include the following: U.S. Patent 5,260,422 to Clark et al.; McCluskey et al., *J. Immunol.*, 141:1451-1455 (1988); WO 93/10220 to Selick et al.; and U.S. Patent 5,338,532 to Tomalia et al.

6. I disagree with those claim rejections. In particular, U.S. Patent 5,260,422 to Clark et al. does not disclose or render obvious the multivalent MHC fusion complexes recited in the subject application which include a MHC molecule that contains a presenting peptide covalently linked to the MHC peptide, wherein the presenting peptide is encoded by nucleic acid sequence encoding a leader sequence attached to the presenting peptide. In fact, the Clark et al. patent teaches that the leader sequence is dispensable in a MHC complex with a covalently linked presenting peptide. For example, the Clark et al. patent describes an MHC construct in which the leader sequence has been removed and replaced by sequence encoding the antigenic peptide (see Clark et al. at column 13, lines 26-34). Accordingly, the Clark et al. patent teaches away from the claimed multivalent MHC fusion complexes by advocating the removal of the leader sequence. None of the McCluskey, Selick or Tomalia references disclose or render obvious the benefits of adding the leader sequence to the claimed multivalent MHC fusion complexes.

7. In addition, the Clark et al patent does not disclose or render obvious the multivalent MHC fusion complexes recited in the subject application which comprise a MHC molecule that contains a peptide-binding groove and a presenting peptide covalently linked to the MHC peptide and positioned such that the presenting peptide can work. The Clark patent does not provide for a linker sequence interposed between the MHC molecule and the presenting peptide.

8. Instead, the Clark et al. patent reports directly linking a sequence encoding an autoimmune peptide AChR 195-215 to the N-terminus of either the I-A^b-alpha or I-A^b-beta chain (see Clark et al. at column 13, lines 17-28) or to the DR2-beta chain (see Clark et al. at column 13, lines 34-37). The Clark et al. patent provides no specific teaching or suggestion for a linker sequence to effectively position the autoimmune peptide in the MHC peptide binding groove.

9. The Clark et al. patent also does not exemplify in the examples or otherwise the preparation of a MHC molecule with a covalently linked presenting peptide.

10. Indeed, the above-mentioned protocol described in the Clark et al. patent would not be expected to generate a functional MHC molecule that could be used to make the claimed multivalent MHC fusion complex. Thus, as disclosed in the present application at page 13, line 11 through page 14, line 28, for instance, the length needed to effectively join the C-terminus of the antigenic or presenting peptide to the N-terminus of an MHC class II-beta chain, i.e. without disrupting the structure of the MHC molecule and to provide an active molecule, is at least about 30 angstroms. That required spanning distance corresponds to a peptide linker sequence interposed between the C-terminus of the presenting peptide and the N-terminus of the MHC class II-beta chain of at least about 10 amino acids.

11. As discussed above, the only description in the Clark et al. patent of a specifically linked peptide is of AChR 195-215. It has been disclosed that the minimum region of the AChR 195-215 peptide capable of binding the MHC molecule and stimulating T cell responses lies between amino acids 199-210. See Kirshner, S.L. et al., 1994, *Cell. Immunol.*, 157:11 (copy attached). Thus, the system reported in the Clark et al. patent, with the AChR 195-215 peptide linked to the N-terminus of the MHC class II-beta chain, would not have the required minimum 10 amino acid linker sequence interposed between the bound region of the peptide antigen and the MHC component.

12. Additionally, even if an MHC molecule that contained an autoimmune peptide covalently linked to an MHC molecule was prepared according to the protocol disclosed in the Clark et al. patent, a functional MHC peptide would not be expected because the autoimmune peptide would not be effectively positioned in the binding cleft or groove of the MHC molecule. In that case, one would not know why the covalently linked MHC molecule was not functional. In particular, one would not have known that the molecule was not functional due to incorrect positioning of the autoimmune peptide in the absence of an interposed linker sequence. In fact, one would assume that the lack of function was due to the presence of the covalent linkage between the autoimmune peptide and the MHC molecule. That conclusion would be reinforced by the Clark et al. patent as it does not exemplify a functional MHC molecule that has a covalently linked peptide.

13. As I also understand the Office Action, the Examiner has taken the position that it would be obvious to use certain methods taught by the McCluskey reference for a chimeric MHC class I/Q10 molecule to make the claimed composition having an MHC class II molecule that contain a presenting peptide.

14. I disagree with that position. As I understand them, the chimeric class I/Q10 molecules of McCluskey are different from the claimed MHC class II molecules. For instance, an MHC class II molecule is a heterodimer consisting of α and β chains. The α chain contains $\alpha 1$, $\alpha 2$, transmembrane and cytoplasmic domains. The β chain contains $\beta 1$, $\beta 2$, transmembrane and cytoplasmic domains. The $\alpha 1$ and $\beta 1$ domains interfold and together form the peptide binding pocket. Peptide interaction with this pocket is required to generate a complex capable of modulating peptide antigen-restricted T-cell responses. The $\beta 2$ domain is required for other functions such as binding to CD4.

15. In marked contrast to MHC class II molecules of the invention, the MHC class I moleculea heterodimer of α and $\beta 2$-microglobulin chains. The α chain contains $\alpha 1$, $\alpha 2$, $\alpha 3$, transmembrane and cytoplasmic domains. The $\beta 2$-microglobulin is a soluble molecule that associates and stabilizes the class I α chain. The MHC class I molecule only utilizes the single α chain (i.e. $\alpha 1$ and $\alpha 2$ domains) to form the peptide binding pocket. The $\alpha 3$ domain is required for binding to CD8 rather than CD4.

16. There are other differences between the chimeric molecule of the McCluskey reference and MHC Class I or Class II molecules. For instance, McCluskey's molecules are reported to be a composite of MHC class I domains and non-classical MHC-like domains that are not comparable to the MHC class II molecules. More specifically, the chimeric molecules of the McCluskey reference contain MHC class I $\alpha 1$ and $\alpha 2$ domains genetically linked to the $\alpha 3$ domain and C-terminus of a different protein, the secreted non-classical MHC-like Q10b molecule. These non-classical MHC domains are not found in the molecules of the present invention nor is there any specific teaching or suggestion in McCluskey to include them in MHC class II molecules.

17. There are other substantial differences between the molecules reported in the McCluskey reference and MHC molecules. For instance, it is known that the $Q10^b$ $\alpha 3$ domain has a different amino acid sequence and glycosylation structure than the native MHC class I $\alpha 3$ domain. In addition, and as compared to MHC class I $\alpha 3$ domain, the non-classical MHC $\alpha 3$ domain shows a number of functional differences including the ability to interaction with the peptide-antigen processing machinery and with CD8. There is no specific teaching or suggestion in McCluskey to use these structurally different molecules to make the MHC class II molecules of the invention.

18. There are other important differences between McCluskey's chimeric molecules and those of the invention. For instance, the McCluskey reference describes the alloreactive elements of the chimeric molecules and shows that multivalent preparations of the chimeric H-$2D^d$/$Q10^b$ molecules stimulated an alloreactive T-cell hybridoma. These T-cells recognize a portion of the H-$2D^d$ $\alpha 1$-$\alpha 2$ fragment of the chimeric molecule. That is, McCluskey's chimeric molecules work **without presenting peptide antigen**. The McCluskey reference does not show that the multimeric chimeric molecules could present peptide antigens to stimulate peptide antigen-specific T-cell responses. Thus one reading McCluskey would assume that the chimeric molecules disclosed by the reference do not contain presenting peptide and are not capable of modulating peptide antigen-reactive T-cell responses.

19. In particular, one would not know if the chimeric H-$2D^d$/$Q10^b$ chain reported by the McCluskey reference folds properly to form a functional peptide-binding groove or whether the chimeric molecules interact properly to present peptide antigen. McCluskey does not report

that the chimeric H-2D^d/Q10^b molecules contain a functional peptide-binding groove or that the multivalent preparations of this chimeric molecule contain presenting peptide. One would assume from McCluskey that the multimeric chimeric molecules do not contain presenting peptide effectively positioned in a peptide-binding grove. The invention molecules have this presenting peptide and it is required for activity. Furthermore, McCluskey's chimeric molecule does not contain domains that are functionally equivalent to the MHC class II β2 domain and thus, do not interact with CD4 as would the claimed molecules.

20. As I understand the chimeric molecules of McCluskey and the claimed MHC class II fusion complex of the invention, the chimeric molecule consists of MHC class I/MHC-like hybrid that is capable of stimulating class I-alloreactive T-cells, whereas the MHC fusion complex consist of class II α and β chains that form a functional peptide binding pocket and an associated peptide antigen. Unlike McCluskey's chimeric molecules, the MHC class II molecules of the invention are capable of modulating peptide antigen-reactive T-cell responses. Another substantial difference is that the MHC class II molecule contains functional domains (i.e. the β2 domain) that are not present in chimeric molecule of McCluskey.

21. As I further understand the McCluskey reference, there is nothing in it that paper that teaches or suggests that given the substantial structural and functional differences between chimeric class I/Q10 molecules and class II molecules, that it would be obvious to use methods in that reference to make the claimed multivalent MHC fusion molecules.

22. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10.29.03

Peter Rhode

Peter Rhode